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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/712,892	11/12/2003	Avi J. Ashkenazi	P5032R1	9438

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EXAMINER	
JOYCE, CATHERINE	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/712,892	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Catherine M. Joyce	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-29* is/are pending in the application.

4a) Of the above claim(s) *23-26,28 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21, 22, and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. Claims 1-20 have been canceled.

2. Claims 21-29 are pending, and claims 23-26 and 28-29 are withdrawn from consideration as being drawn to a non-elected invention

3. Claims 21, 22 and 27 are under examination.

4. Applicant's election without traverse of the species of "determining the level of expression of the gene using an oligonucleotide in an RT-PCR analysis" and "the samples are obtained from colon tissue" in the reply filed on December 13, 2005 is acknowledged.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 27 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single,

simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claim 27 is drawn to a method of diagnosing the presence of a tumor in a mammal, the method comprising determining the level of expression of a gene encoding the polypeptide shown as SEQ ID NO:22 in a test sample of tissue cells obtained from the mammal and in a control sample of normal tissue cells of the same tissue type as the test sample, wherein a higher level of expression of the gene in the test sample, as compared to the control sample, is indicative of the presence of a tumor in the mammal from which the test sample was obtained, wherein the test and control samples are obtained from colon tissue.

The specification contemplates methods of diagnosing the presence of a tumor in mammal comprising determining the level of expression of a Tumor-associated Antigenic Target (TAT) polypeptide (page 7, lines 29-31). The specification teaches that a polynucleotide encoding the TAT400 polypeptide of SEQ ID NO:22 shows an up regulation of expression in colon tumor as compared to normal colon tissue, as determined by an analysis of a database containing gene expression information, wherein the database is the GeneExpress database (Gene Logic Inc.) (Example 1, pages 117-119). The specification also teaches that an analysis using a 5' nuclease assay and real-time quantitative PCR indicated that a polynucleotide encoding the TAT400 polypeptide was at least two-fold over expressed in colon tumor tissues as compared to normal colon tissues (Example 2, pages 119-120). The specification also teaches that an in vitro hybridization analysis indicated that 2/2 colorectal carcinomas were strongly positive for expression of a polynucleotide encoding the TAT400

polypeptide (Example 3, pages 120-122). The specification also teaches that a tissue expression profile analysis, conducted by searching an expressed sequence tag (EST) DNA database determining the expression profile of a gene based upon its proportional correlation with the number its occurrences in EST databases, indicated high tissue expression and significant up-regulation of expression of a polynucleotide encoding the TAT400 polypeptide in colon tumors (Example 4, pages 122-125).

It is noted that the TAT400 polypeptide of SEQ ID NO:22 is the same as the human cadherin 11 precursor protein, also known as osteoblast-cadherin or OB-cadherin, as indicated by the UniProtKB/Swiss-Prot entry P55287, enclosed herewith. A sequence search comparison that shows the identity of SEQ ID NO:22 with the cadherin 11 precursor protein described in UniProtKB/Swiss-Prot entry P55287 is attached herewith as an Appendix to this Action.

The specification cannot be reasonably extrapolated to enable the claim because one of skill in the art could not predict, and would not expect, that determining the level of expression of a gene encoding the polypeptide shown as SEQ ID NO:22 in a test sample of tissue cells obtained from a mammal and in a control sample of normal tissues cells of the same tissue type as the test sample, wherein a higher level of gene expression in the test sample as compared to the control sample, is indicative of the presence of a colon tumor in the mammal from which the test sample was obtained for the following reasons: (i) the art shows that the upregulation of cadherin 11 expression in diseases of the colon that are not tumors; and (ii) the art teaches that an upregulation of cadherin 11 expression levels is not found in colon adenocarcinomas.

In the first aspect, Costello et al. (2005, PLOS Medicine 2(8):0771-0787) teaches that high density cDNA microarray analysis of sigmoid colon biopsy samples of patients with inflammatory bowel disease (IBD) (including both patients with ulcerative colitis and Crohn's disease), and subsequent confirmation of results by real-time PCR analysis (page 0771), indicated that cadherin 11 is upregulated in both types of IBD. As demonstrated by Costello et al., an up regulation of cadherin 11 expression may

indicate a disease of the colon such as Crohn's disease or ulcerative colitis. The specification does not teach how to differentiate between tumors and other diseases. Therefore, it cannot be predicted that the up regulation of cadherin 11 expression levels in a test colon tissue sample as compared to expression levels in a normal colon tissue sample would predictably indicate the presence of a tumor.

In the second aspect, Munro et al. (1995, Experimental and Molecular Pathology 62:118-122) teaches that a semiquantitative analysis of OB-cadherin (also known as cadherin–11) RNA expression levels indicates that OB-cadherin RNA expression levels are similar in normal colon and colon adenocarcinomas (page 119). Further, Morimoto et al. (2004, Oncogene 23:1618-1626) teaches that an analysis of cadherin-11 expression in archived human tumors indicated that cadherin-11 was not detected in colon adenocarcinoma cells (page 1622, first column). Given the contradictory finding in the art, it cannot be predicted whether an analysis of cadherin 11 expression in a colon tumor/colon adenocarcinoma tissue sample as compared to expression levels in a normal colon tissue sample would result in a reliable finding of over expression of cadherin 11 in the tumor sample as compared to normal, or whether, in fact, colon adenocarcinomas could be diagnosed with the instantly claimed method.

In view of the teaching in the art that polynucleotides that encode cadherin-11 are up-regulated in diseases of the colon that are not colon tumors and that polynucleotides that encode cadherin 11 in are not upregulated in colon adenocarcinomas, one of skill in the art could not predict that assessing the levels of polynucleotides that encode cadherin 11 would be useful in diagnosing the presence of a colon tumor. Thus, practice of the claimed invention would require undue experimentation.

7. Claim 22 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing the presence of a tumor in a mammal comprising determining the level of expression of a gene encoding the polypeptide shown as SEQ ID NO:22 in a test sample of tissue cells obtained from the

mammal and in a control sample of normal tissue cells of the same tissue type as the test sample, wherein the step of determining the level of expression of the gene comprises employing two oligonucleotides in an RT-PCR analysis, does not reasonably provide enablement for a method of diagnosing the presence of a tumor in a mammal comprising determining the level of expression of a gene encoding the polypeptide shown as SEQ ID NO:22 in a test sample of tissue cells obtained from the mammal and in a control sample of normal tissue cells of the same tissue type as the test sample, wherein the step of determining the level of expression of the gene comprises employing an oligonucleotide in an RT-PCR analysis.

Claim 22 is drawn to a method of diagnosing the presence of a tumor in a mammal, the method comprising determining the level of expression of a gene encoding the polypeptide shown as SEQ ID NO:22 in a test sample of tissue cells obtained from the mammal and in a control sample of normal tissue cells of the same tissue type as the test sample, wherein a higher level of expression of the gene in the test sample, as compared to the control sample, is indicative of the presence of a tumor in the mammal from which the test sample was obtained, wherein the step of determining the level of expression of said gene comprises employing an oligonucleotide in an RT-PCR analysis.

The specification teaches as set forth above. The specification also teaches that when PCR is employed, oligonucleotides that define the desired termini of the DNA fragment are employed as the 5' and 3' primers in the PCR (page 84, lines 4-7), and that two olignucleotide primers are used to generate an amplicon typical of a PCR reaction (page 119, lines 31-32).

The teaching of the specification cannot be reasonably extrapolated to the scope of the claims because one of skill in the art could not predict, and would not expect, that determining the level of expression of the claimed gene with a single oligonucleotide in an RT-PCR would function as claimed. The specification teaches both 5' and 3' primers are employed in PCR and that two oligonucleotide primers are used generate an

amplicon typical of a PCR reaction. In view of this teaching in the specification, one of skill in the art could not predict that the invention would function as claimed when employing a single oligonucleotide in an RT-PCR analysis. Thus, practice of the invention would require undue experimentation.

Claim Rejections - 35 USC § 102

8. The following is a quotation of 35 U.S.C. 102(e) which forms the basis for all obviousness rejections set forth in this Office action:

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 21 and 22 are rejected under 35 U.S.C. 102(e) as being unpatentable over US Patent No. 6,680,175 (filed January 20, 1999; issued January 20, 2004), as evidenced by UniProtKB/Swiss-Prot entry P55287.

The claims are drawn to the following: a method of diagnosing the presence of a tumor in a mammal, the method comprising determining the level of expression of a gene encoding the polypeptide shown as SEQ ID NO:22 in a test sample of tissue cells obtained from the mammal and in a control sample of normal tissue cells of the same tissue type as the test sample, wherein a higher level of expression of the gene in the test sample, as compared to the control sample, is indicative of the presence of a tumor in the mammal from which the test sample was obtained (claim 21), wherein the step of determining the level of expression of the gene comprises employing an oligonucleotide in an RT- PCR analysis (claim 22).

US Patent No 6,680,175 teaches a method for determining the presence or absence of metastatic cancer in a patient comprising the steps of (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a

polynucleotide encoding OB-cadherin and (b) detecting in the sample a level of a polynucleotide that hybridizes to the oligonucleotide, relative to a predetermined cut-off value, and therefrom determining the presence or absence of a metastatic cancer in a patient (column 2, lines 46-55). US Patent No 6,680,175 also teaches that in a preferred embodiment, the cut-off value for the detection of a metastatic cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without a detectable cancer (column 19, 27-37). US Patent No. 6,680,175 also teaches that cancer is significant problem among men and women (column 1, lines 22-67). Thus, one of skill in the art would instantly recognize that the term patients includes humans, a mammal. US Patent No 6,680,175 also teaches that the amount of mRNA may be detected via polymerase chain reaction using an oligonucleotide primer that hybridizes to a polynucleotide that encodes OB-cadherin or a complement of such a polynucleotide (column 2, lines 55-59). US Patent No 6,680,175 also teaches the RT-PCR analysis of OB-cadherin expression (Example 2, column 2, lines 6-52). As evidenced by the UniProtKB/Swiss-Prot entry P55287, the TAT400 polypeptide of SEQ ID NO:22 is the same as the human cadherin 11 precursor protein, also known as osteoblast-cadherin or OB-cadherin. Thus, all of the claim limitations are met.

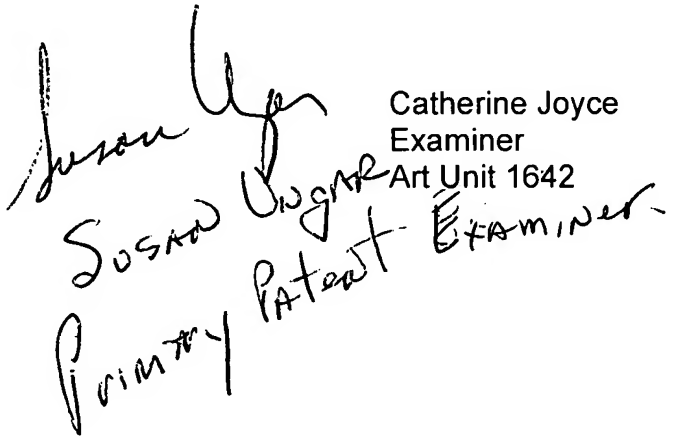
10. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine M. Joyce whose telephone number is 571-272-3321. The examiner can normally be reached on Monday thru Friday, 10:15 - 6:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Catherine Joyce
Examiner
Art Unit 1642